

THE PHARMACOLOGY OF NEWER AGENTS EMPLOYED IN THE TREATMENT OF GASTROINTESTINAL DISTURBANCES WITH SPECIAL REFERENCE TO REGIONAL ILEITIS AND ULCERATIVE COLITIS*

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IT is a genuine pleasure and distinct honor to participate with Drs. Almy and Hinton in this Symposium which deals with the very important problem of regional ileitis and ulcerative colitis. It falls to my lot to discuss briefly with you the pharmacology of the newer drugs for the treatment of these diseases.

Perhaps the title might just as well have been Regional Ileitis or Ulcerative Colitis as far as therapeutic agents are concerned since those drugs used in the former condition are so often used in the latter, and vice versa. In fact, there are some authorities who consider these diseases to be synonymous but manifested in different intestinal areas, or to stem from the same disturbed physiologic background, hence the terms: regional ileitis, regional enteritis, skip areas, ileocolitis, acute and chronic idiopathic colitis or non-specific ulcerative colitis, etc. More recently the term, "sacral parasympathetic ulcerative colitis" has been applied by Portis,¹ to that lower colonic area under exaggerated sacral parasympathetic neural control, a disturbance from which, he believes, may stem all colitis by creeping upward along the colon. For our purposes tonight we should prefer to concern ourselves chiefly with the pharmacology of those newer therapeutic agents, the value of which has been demonstrated. We should also like to suggest for your consideration another therapeutic approach to the problem based on the pathophysiology of this condition.

There is general agreement on the presenting symptoms and findings of ulcerative colitis; these include abdominal pain and griping, diarrhea

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which is often profuse, frequent and bloody, high bacterial content of the stools, weight loss which is sometimes severe, fever and general malaise associated with anemia and malnutrition. There also seems to be quite general agreement on the unknown cause of this condition. Ross-miller and Messenger² state: "Failures in management are due primarily to the fact that the cause of regional ileitis (and ulcerative colitis?) is unknown." It is the consensus that there is no primary infecting organism etiologically responsible for chronic nonspecific ulcerative colitis, and in terms of specific agents, therefore, therapy is directed toward the control of the secondary invaders since they are probably chiefly responsible for the fever with its associated diarrhea and dehydration. The chief, if not the only, exception to this idea of unknown cause of the disease is that of dysentery and ulcerative enteritis due to, or associated with amebiasis, for which obviously there is specific therapy available in the form of emetine hydrochloride and other newer specifically acting agents.

In the medical management of this disease, discussed by Dr. Almy, he has referred to sulfa drugs and the newer antibiotics for the control of secondarily invading organisms responsible for so many of the symptoms. The old list of therapeutic agents is long, but most of its members are obsolete, now that well tolerated chemotherapeutic agents in the form of the newer antibiotics have proved their value for the control of secondary infection.

Since the advent of the antibiotics many authorities have discarded the use of such sulfa drugs as sulfapyridine, sulfaguanidine, sulfadiazine and sulfathalidine but as yet this is not a universally accepted custom because there are those who believe that conjoint therapy consisting of certain sulfa preparations with antibiotics, affords better control of the secondary infection than by either alone. This is still a moot point but justifiable when one considers the probability of pharmacologic potentiation of one type of agent by the other, a feature which so often can be demonstrated when employing different types of pharmacologic agents for other diseases.

The *pharmacology* of these *newer* chemotherapeutic agents is quite well established but it may be pertinent to remind ourselves that dangers still abide, even though less frequently than earlier, with the promiscuous use of such agents. The sulfa drugs, even sulfadiazine and sulfathalidine, may still cause nausea and vomiting or potentially such undesirable

accidents as drug or allergic reactions, and agranulocytosis, even though very rarely. The same holds true to lesser and varying degrees for the more recently developed antibiotics, aureomycin, chloramphenicol and terramycin. These agents may *potentially* present serious types of "drug symptoms" but in differing frequency and perhaps lessened severity. May we hasten to add, however, that the antibiotics just cited have proved to be very safe, but drugs, being what they are, foreign bodies, we must anticipate that with widespread usage, some of these aberrant or toxic manifestations, even though rare, will appear.

No doubt such factors as variability of absorption associated with intestinal motility, the amounts of pus, mucoid secretion and blood present, and the predominance of certain types of secondary infectious organisms will demand, in some cases, much larger doses of antibiotics than normally employed. Should absorption of such increased dosage be more abrupt than anticipated, rather early exacerbation of nausea and vomiting and general malaise might be encountered with some antibiotics. Such might well be the case if antispasmodics were to be suddenly included in the drug regime for the relief of cramps and intestinal griping, thus retarding intestinal motility and permitting greater and more rapid absorption in some cases.

The danger of too rapid absorption of the antibiotic may be diminished to some extent by its incorporation in, and simultaneous administration with, one of the available cellulose preparations.³ Experience demonstrates that such a colloidal vehicle is desirable because it permits not only rather steady release of the antibiotic but also tends by its viscous characteristics to cushion the inflamed intestinal mucosa, with its exposed sensory dendrons, against the irritating properties of these newer agents. Such irritation of the gastrointestinal tract may lead to reflex nausea and vomiting, to hyperperistalsis and griping, and these reactions may be favorably affected by the demulcent mixture of the antibiotic in any one of the available protective celluloses. Various preparations of colloidal aluminum hydroxide have been employed in a similar manner with success; they tend to defeat irritation by their demulcent and mild astringent properties in the intestine, but this feature is often unbalanced by the difficulty of releasing effective titers of the antibiotic for the situation at hand.⁴ Therefore, the celluloses (or even milk or Pepto-Bismol) may be used in preference, since they do not interfere so markedly in releasing the antibiotic and limiting absorption

TABLE I — AUREOMYCIN: 750 MG. FOUR TIMES PER DAY, BY MOUTH

Case	Diagnosis	Days Admin.	Smears*			Cultures**				
			+	—	Yeasts	<i>E. Coli</i> <i>A. Aerog</i> <i>S. Faecalis</i>	Spores	<i>Pro-</i> <i>teus</i>	<i>Pseudo-</i> <i>Monas</i>	Yeasts
17	Ileocolitis	2½	0	1+	1+	0	Absent	0	1+	1+
18	Ca. rectum	2¾	0	2+	1+	0	Absent	0	4+	4+
19	Ca. rectosigmoid	2¾	0	0	2+	0	Absent	0	0	4+
20	Ca. sigmoid	2¾	0	2+	1+	0	Absent	4+	0	0
21	Regional Enteritis	2¾	0	0	1+	0	Absent	0	0	4+
22	Ileocolitis	2¾	0	0	1+	0	Absent	0	0	4+
23	Ca. Spl. Flex. Colon	2¾	0	0	3+	0	Absent	0	1+	4+
24	Ca. Rectum	2¾	0	2+	1+	0	Absent	4+	0	0
25	C.U.C.	2½	0	1+	0	0	Absent	4+	0	0
26	Reg. Ileocolitis	3	0	1+	1+	0	Absent	2+	0	0
27	Ca. Rectum	3	0	0	1+	0	Absent	0	0	4+
28	Perf. Divert. Sig. Vesical Fist.	3¼	0	2+	2+	0	Absent	0	4+	0
29	C.U.C.	3½	0	0	2+	0	Absent	0	0	4+
30	Ca. Sigmoid	3½	0	1+	1+	0	Absent	0	0	4+
31	Ileocolitis	3½	0	0	2+	0	Absent	0	0	4+
32	Ca. Sigmoid	3½	0	0	2+	0	Absent	0	0	4+
33	Ca. Trans. Colon	3½	0	1+	1+	0	Absent	0	0	2+
34	Ca. Rectosigmoid	3½	0	3+	1+	0	Absent	4+	0	1+
35	Ca. Rectum	3½	1+	0	2+	0	Absent	0	0	4+
36	Ca. Rectum	3½	0	0	2+	0	Absent	0	0	4+

* The approximate numbers of bacteria were recorded as follows: 1+, 1 microbe in several fields (x980); 2+, from 1 to 10 microbes per field; 3+, numerous organisms per field; 4+, myriads of organisms per field.

** The approximate numbers of bacterial colonies per plate were indicated as follows: 1+, 5 or less; 2+, 6 to 50; 3+, 51 to 200; 4+, more than 200.

(Dearing, W. H. and Heilman, F. R., Proc. Staff Meet. Mayo Clin. 25: 91, Feb. 15, 1950.
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by the mucosa^{3, 5, 6} while simultaneously exercising their favorable protective effects on the highly sensitive inflamed mucosa.

The effect of aureomycin on fecal bacterial flora in ulcerative colitis and other intestinal diseases, is well represented by Table I.⁷ After two or three days of oral treatment, one notes the early and complete disappearance of *E. coli*, *A. aerogenes*, and *Streptococcus faecalis*; this is quite typical but not true of all cases. Furthermore such "bowel sterilization" is often only temporary despite sustained therapy. Note that there seems to be an associated predominance of yeasts; actually there is an increase in yeast content when cultured, which fact had early forecast the potential dangers of prolonged aureomycin therapy as verified

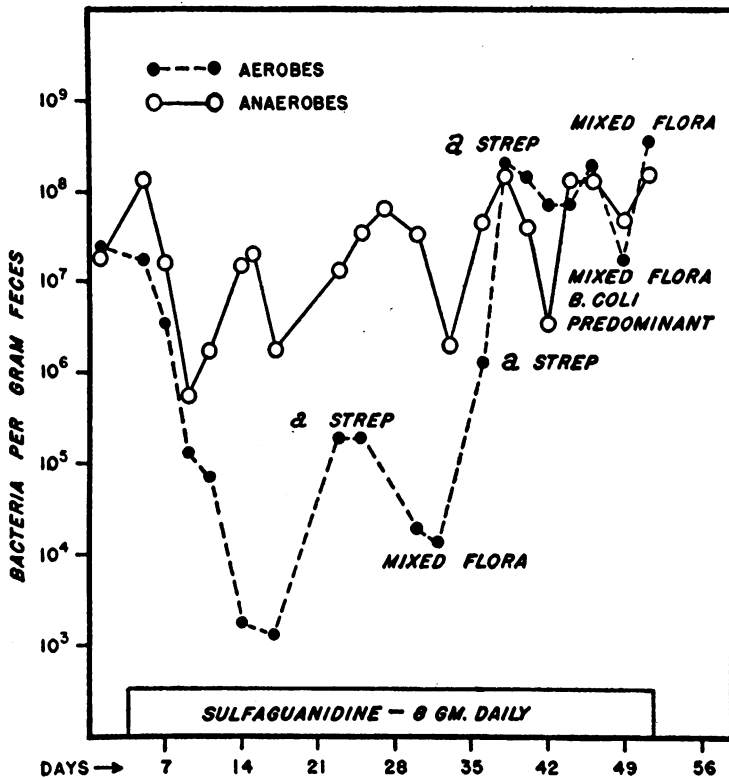


Fig. 1—Effect of sulfaguanidine on bacterial flora in ulcerative colitis. (Marshall, H. C., Jr., et al, J.A.M.A., 144: 900, Nov. 11, 1950. Reprinted by permission from the J.A.M.A.)

recently by the appearance of fungal infections of the liver and other areas.⁸

The work of Marshall and his associates⁹ as presented in Figures 1 and 2, indicates the potential danger associated with prolonged therapy by sulfaguanidine and by the newer antibiotic agents; a varying degree of resistance is developed by certain organisms normally present in the gastrointestinal tract and this fact obviously becomes of major import when considering the use of these drugs in preparing the patient with ulcerative colitis or regional ileitis for surgery.

Marshall and his associates⁴ conclude in part as follows:

“A fecal bacterial flora resistant to sulfonamides, penicillin, streptomycin, aureomycin and chloromycetin develops in patients with chronic

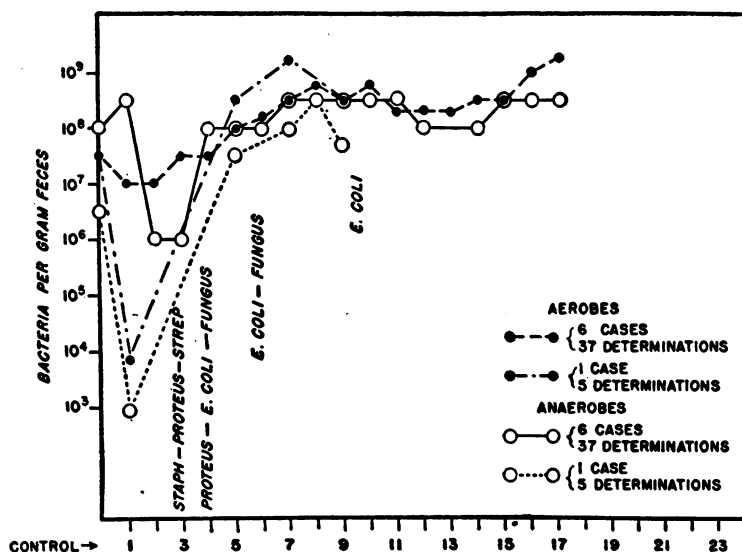


Fig. 2—Bacterial flora in ulcerative colitis during chloramphenicol therapy. (Marshall, H. C., Jr., et al, J.A.M.A., 144: 902, Nov. 11, 1950. Reprinted by permission from the J.A.M.A.)

ulcerative colitis after varying periods of continued administration of these drugs.

“Average aerobic bacterial counts seemed to rise above control levels after varying lengths of time of oral administration of penicillin, streptomycin, aureomycin and chloromycetin.*

“The bacteriologic studies suggest that chemotherapeutic agents should be reserved for the infectious complications of the disease and be limited in duration to prevent the development of a resistant fecal flora.”

Regarding the *mechanism of action* of the chemotherapeutic agents discussed, there is little that can be said except to emphasize two facts: *first*, the sulfa drugs *still act* apparently by interfering with PABA (paraminobenzoic acid) and its assimilation or utilization by the bacterial cell as one of its nutrient materials, thus literally starving it to death, and, *second*, despite much theorization no similar, known, clean-cut competitive inhibition seems to prevail in reference to the antibiotics. It is thought that chloramphenicol may act against typhus organisms by “wrapping

* There is no reason to anticipate that terramycin would behave differently.

itself around the bacterial wall," so to speak, interfering thus with bacterial enzymic features and metabolism in general. Specifically, chloramphenicol is known to inhibit glutamate assimilation¹⁰ and to disturb nucleic acid metabolism;¹¹ J. Marmur and A. K. Saz¹² tentatively conclude that "chloramphenicol inhibits the synthesis of the adaptive enzymes which initiate the dissimilation of gluconate." Likewise, terramycin is capable of blocking the utilization of ribonucleic reserve by *E. coli*.¹³ It is highly probable that aureomycin may exert similar embarrassment of certain metabolic activities.

The pharmacologic mechanism of relief, *when afforded*, by hog's stomach and intestine is not known. Gill¹⁴ contends that they act by replacing some vital component absent or deficient in ulcerative colitis, but this remains to be proved.

Intense interest accompanied the finding of increased lysozyme content of the stool of the patient with ulcerative colitis. There soon followed the use of agents to inhibit lysozyme activity, in the form of sodium hexadecyl sulfate and of Aerosol OT (a detergent) but their pharmacology need not be discussed in view of Machella's potent statement¹⁵ that "the inhibition of lysozyme (by these agents) does not alter the clinical course of the disease."

Intestinal griping and cramps can still be quite well controlled by anticholinergic blocking agents like atropine or some of its synthetic substitutes; if insufficient in effect they can be supported by codeine or Demerol but preferably not by morphine because one of the pharmacodynamic features of the latter is its capacity to constrict the smooth muscle of the intestine,¹⁶ and cases of "silent perforation" of ulcerated areas have been reported.

You will note that we have not referred to the action of ACTH and cortisone in these diseases, chiefly because their value is still equivocal, despite some encouragement; likewise, their basic mechanisms of action in these diseases have not been clarified. Hence there is little that one can say at the moment regarding their pharmacology in ulcerative colitis.

Successful though antibiotic and antispasmodic therapy may be, such relief is all too frequently of only a temporary nature. This leads one to believe that the underlying cause of ulcerative colitis must be *re-searched*. Particularly is this true when one realizes and appreciates the excellent results reported after psychotherapy by Grace and Wolff¹⁷

and others, as employed in severe, refractory cases in which the stools were bloody and diarrheic in nature, but *free* of pathogenic organisms or amebae! There may well be logic in the approach of Portis¹ who considers that treatment should be early directed to the element of cholinergic predominance (that is, sacral parasympathetic influence) leading to the condition which he describes as "sacral parasympathetic ulcerative colitis." (In view of remarks to follow, a better term may prove to be "Sacral *Autonomic* Ulcerative Colitis.") "Medical neurectomy" by means of atropine or its substitutes may give temporary relief (along with antibiotics for the control of secondary infection) but either surgical neurectomy, as exercised by Shafiroff and Hinton¹⁸ or surgical resection of the distal colon in this special situation may have to be resorted to if psychotherapy and medical management do not control this condition.

We therefore return to the pathologic picture of ulcerative colitis which is characterized by:

Edema (engorgement)

Readily bleeding areas on slight contact

Friable mucosa

These could well be the reflection or the result of cholinergically induced smooth muscle spasm leading in turn to tissue ischemia and hypoxia,¹⁹ thence to increased capillary permeability associated with hypoxia and improper metabolism and function of mucosal tissues. Also, edema and easily provoked bleeding could indicate poor venous and lymphatic return, caused by *mechanically* compressed vascular elements in the spastic smooth muscle areas of the intestinal wall. If such intestinal spasm were the chief factor in *noninfectious* ulcerative colitis, atropine and agents acting like it should be more effective than they are in clearing up the edema and engorgement.

It would seem therefore, that another important division of the automatic nervous system to be held suspect in the production of edema, is the "true sympathetic" or thoracolumbar sympathetic portion, the normal counterbalance to the parasympathetic influence, that is, the adrenergic as counterbalanced by the cholinergic system (Fig. 3). Such adrenergic or sympathetic influence is conducted through the splanchnic nerves and sympathetic components of the pelvic plexuses, resulting in relaxation of gastrointestinal smooth muscle, except at the sphincters where contraction results. *Simultaneously*, sympathetic neural impulses

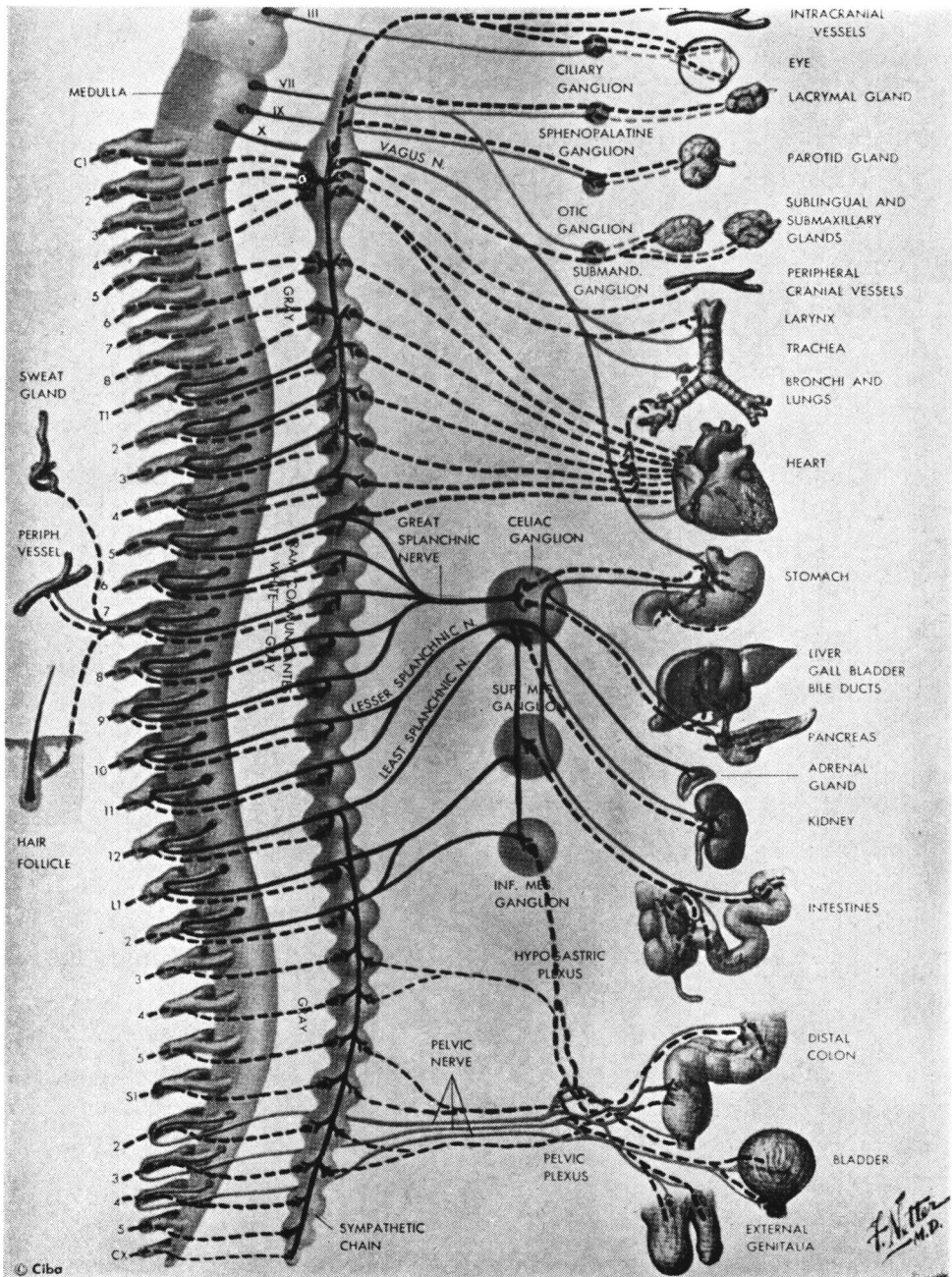


Fig. 3—Schema of the autonomic nervous system.

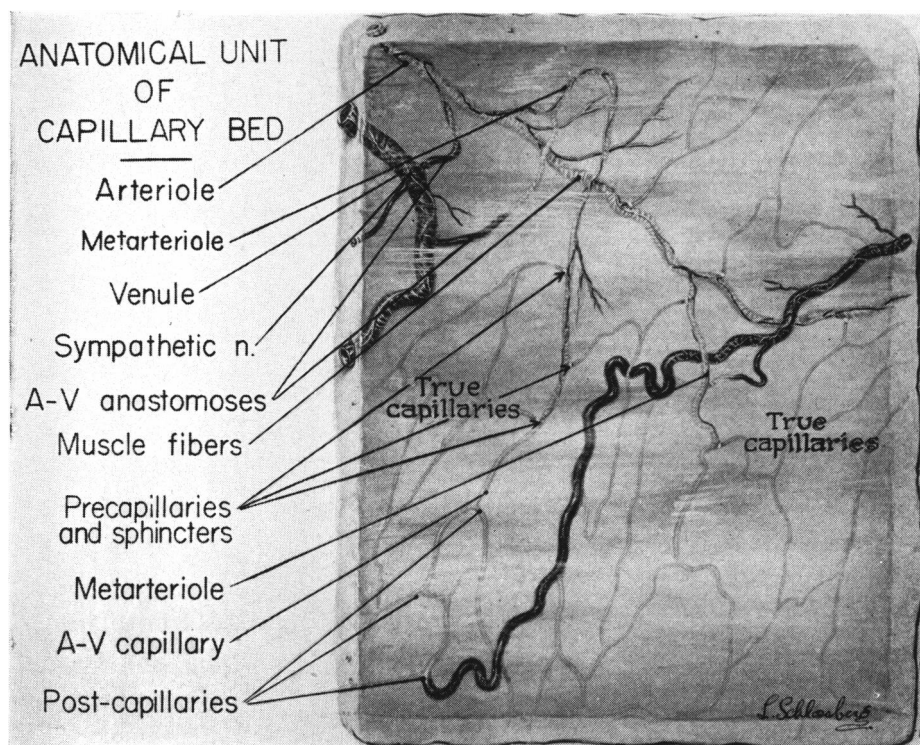


Fig. 4—Supplied through the courtesy of Winthrop-Stearns, Inc.

produce a *constriction* of the *smooth muscle* of all blood vessels in the *intestine*, resulting, *first* in blanching and hypoxia, and constriction of the precapillary sphincters, as demonstrated so well by Lutz and Fulton²⁰ and by Chambers and Zweifach²¹ and others (Fig. 4, 5 and 6). The *secondary* result of such sustained precapillary sphincteric constriction could well be edema, poor lymphatic and venous return, mucosal friability and hemorrhage.

Sustained sympathetic or *adrenergic blockade* by chemicals would seem to be in order and to the best of our knowledge, it has not been attempted as yet except of course in the form of resection. If surgical *parasympathectomy* be in order for varying degrees of relief, surgical *sympathectomy* should likewise seem rational, either by itself or along with parasympathectomy; in fact, such a procedure is actually exercised by Shafiroff and Hinton,¹⁸ since the sympathetic fibers are so intimately interwoven with the parasympathetic in the pelvic plexuses that they

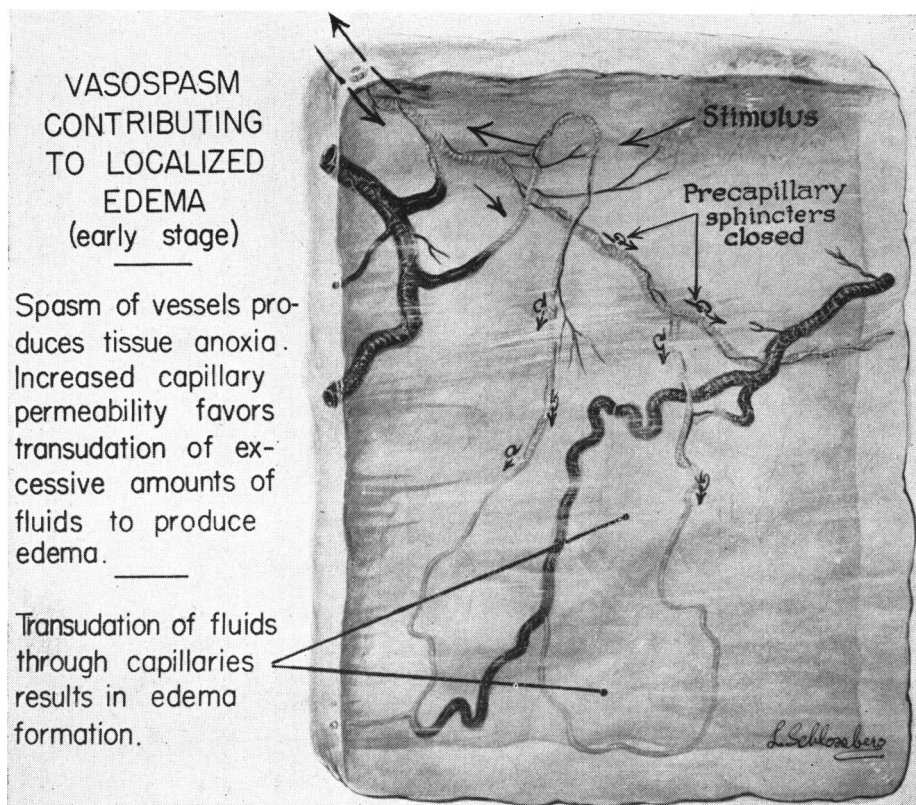


Fig. 5—Supplied through the courtesy of Winthrop-Stearns, Inc.

are both transected in their type of neurectomy. Hence, if *surgical* sympathectomy be justified, then *medical* sympathectomy should likewise seem judicious.

To be sure the engorged, edematous mucosa, under severe emotional stress as precipitated by the examiner, may not always lead to visible blanching. Such areas of temporary blanching as reported by Almy²² may be spotty because they may be, as yet, nonengorged areas even though small; in other words, they may reflect the fact that the precapillary sphincters in these very small areas were, as yet, not involved until insulted by excessive experimental emotional stress while under proctoscopic observation.

We should like to propose therefore that we consider a fresh approach to the problem of ulcerative colitis and regional ileitis, namely

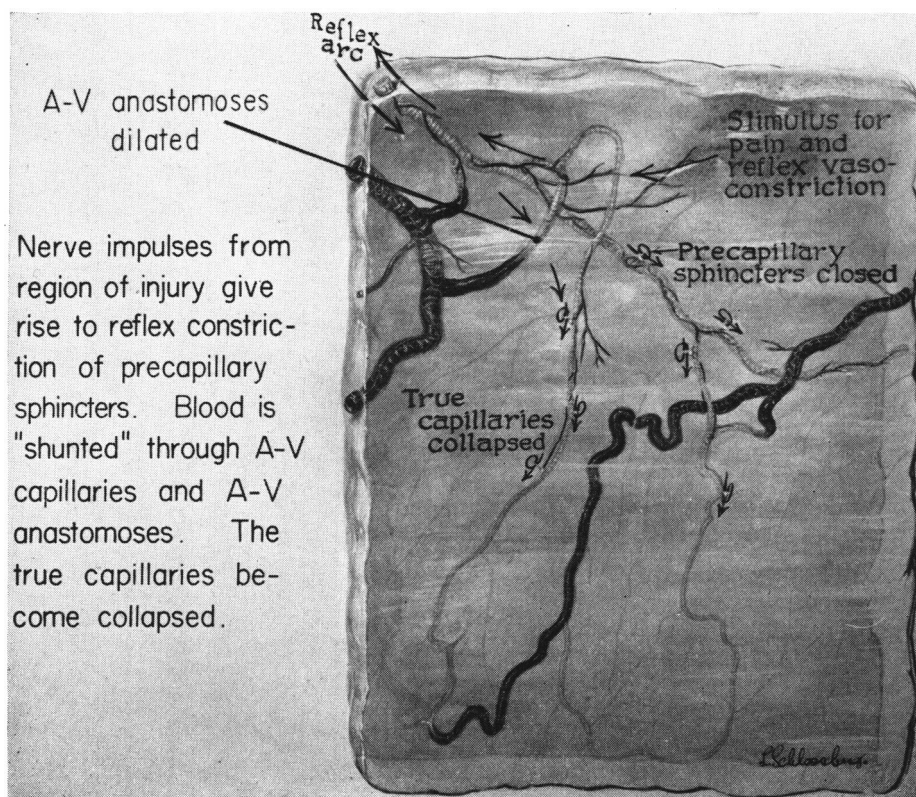


Fig. 6—Supplied through the courtesy of Winthrop-Stearns, Inc.

that from the point of view of sympathetic or *adrenergic predominance* which could well be an *independent* reflection of emotional stress—if you will, a sort of “gastrointestinal Raynaud’s disease.” On the other hand, one might well conceive of such adrenergic predominance occurring simultaneously with excessive cholinergic influence in the same area, the former producing edema by precapillary (and probably venous) constriction, and the latter by mechanical interference due to spasm of smooth muscle in the intestinal wall. Would it not seem logical that if the edema associated with thrombophlebitis of a leg or an arm can be ameliorated by appropriate adrenergic blocking therapy, by breaking precapillary sphincteric spasm, such benefit might likewise prevail if similar agents were to be employed for attacking the edema associated with regional ileitis and ulcerative colitis? There are several such agents available today.²³ These include the following:

Peripheral Blockers

Readily Available

Benodaine (?) (i.v.) (Merck)

Dihydroergot preparations (CCK-179-Sandoz)

Regitine and Priscoline (?) (orally) (Ciba)

Experimentally Available

Ro2-3248 (?) (orally) (Hoffmann-LaRoche)

SY-28 and SY-30 (Parke-Davis)

Lilly-08124, etc. (?) (large series) (Eli Lilly)

Dibenamine (i.v.); SKF 688A (orally) (Smith, Kline and French).

Ganglionic Blockers

Readily Available

Etamon (TEA) (Parke-Davis)

C6 (Hexamethonium)

Experimentally Available

Pendiomide (Ba-9295) (Ciba)

Su-1194 (Ciba)

Arfonad (Hoffmann-LaRoche)

If the concept as presented seems to be well founded, we should like to propose that those of you primarily interested in the diseases under discussion tonight attempt to place the bowel at complete physiologic rest if possible. To do so, one could employ atropine or its substitutes to insulate against acetylcholine's tonic and propulsive influences, and any one of several adrenergic blocking agents to insulate the gastrointestinal blood vessels against adrenergic vasoconstrictive influences. Theoretically, one might choose to use a single agent such as Etamon or hexamethonium, both ganglionic blocking agents which block impulses at the prepost-ganglionic synapse throughout the entire autonomic nervous system, that is, in the parasympathetic as well as the sympathetic pathways. On the other hand, such therapy might well have to be sustained, and in reference to the sympathetic portion of the nervous system in particular, be fortified by peripherally acting adrenergic blockers because of the nature of local disturbance at the precapillary sphincter. Again, to be sure, in the exercise of such a dual approach in the establishment of double "medical neurectomy" one must consider it only as an experimental adjunct to the well delineated fundamentals of Medical Management discussed by Dr. Almy.

The potential role played by adrenergic or sympathetic predominance in these diseases is still unproved from a medical point of view but seems plausible. If it were to be proved untenable, the greater would be the challenge for further research. In the words of Robert Browning, "a man's reach should exceed his grasp, or what's Heaven for?"

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